Appendix F-4
Calculating the Economic Benefits of Reductions in Manganese Air Concentrations
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Assessing Benefits of Reductions in Manganese Air Concentrations

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Introduction

Manganese presents a conundrum for risk assessment because it is both an essential nutrient and a potent neurotoxicant. Its neurotoxic properties have emerged almost exclusively from inhalation exposures, although some epidemiological data suggest that high concentrations in drinking water may be associated with neurological impairment. Several kinds of occupations expose workers to inhaled manganese, the most prominent being mining, ore-crushing, and ferro-manganese production. Mining for manganese ore provides the best documented association owing to the high levels of MnO_2 dust encountered in the process.

Table 1 lists some of the characteristic signs and symptoms of manganese neurotoxicity. Some, like bradykinesia, are also distinguishing signs of Parkinson's disease. Others, like the kind of emotional lability marked by abnormal laughing (and crying), are distinctive for manganese. In South American mining communities familiar with manganese intoxication, such a syndrome has earned the label, "locura manganica," or manganese madness, often viewed as the first stage of the full syndrome of manganese intoxication.

The most suitable animal model for research into manganese neurotoxicity is the nonhuman primate. Because of the unique organization of the primate brain, other animal models, such as rodents, are not as satisfactory, although they may yield useful information about neurochemical processes. Figure 1 depicts these differences as the relationship between dose and measure and shows, roughly speaking, a difference in sensitivity of close to two orders of magnitude between primates and rodents. One factor that may account for some of the discrepancy is the lack of advanced tests for motor function in the rodent studies comparable to the effortful response criterion used by Newland and Weiss (1992) in trained monkeys.

Although the motor signs exhibited by Mn miners correspond in part to those seen in Parkinson's disease (PD), enough differences are visible to question the widely-held proposition that Parkinson's and manganism are virtually identical. Barbeau (1984) suggested that the syndrome more closely resembled a dystonia than classical PD, a point of view also supported by Pat et al (1999) and others. Neuropathological observations support this distinction. With manganism, the main evidence of degeneration is seen in the globus pallidus, with less severe damage in the striatum (putamen and caudate nucleus) and in the substantia nigra pars reticulata. In contrast, the primary lesions seen in PD lie in the substantia nigra pars compacta and consist of depigmented and missing neurons, viewed as the dominant morphological markers of PD, accompanied by Lewy bodies, which consist of abnormally aggregated proteins found largely in dopaminergic neurons and recently shown to also contain the protein alpha-synuclein.

Convincing evidence of globus pallidus involvement also comes from magnetic resonance imaging (MRI) data. Because manganese is a paramagnetic metal, it modifies the return of protons to their original orientation after displacement by a strong magnetic field. These shortened times can then be used to produce different degrees of brightness in the calculated image that are related to local manganese concentration. The images and plots published by Newland et al (1989) and Newland and Weiss (1992) show the highest concentrations in the vicinity of the globus pallidus in exposed monkeys. MR images of an arc welder who had been exposed in the process of repairing and recycling railroad track made of manganese steel alloy also showed localized deposition in the globus pallidus (Nelson et al, 1993).

Ingested manganese is closely regulated by the gut. Inhaled manganese bypasses the gut, and can enter the brain in two ways. First, as described by Tjalve and Henriksson (1999), the olfactory pathways provide a direct path into brain tissue. Rats given ^{54}Mn intranasally accumulated the metal in a variety of brain structures, including the basal ganglia. Primates exposed by inhalation to trace amounts of ^{54}Mn showed a rise in brain levels that peaked at about 40 days (Newland et al, 1987). The manganese disappeared from brain much more slowly, with half-lives of 223 to 267 days in the two monkeys studied. ^{54}Mn was detected in the lungs for 500 days after exposure, suggesting that they served as a reservoir for uptake into brain (Figure 2). Although these data may also reflect some storage in bone, as noted by Andersen et al (1999), they indicate the strong possibility that long residence times in the lung provide a continuing source of brain exposure. This may be a special problem for young children in areas where dense vehicular traffic deposits manganese-laden dust. As with lead (cf., Lanphear et al, 1998), typical children's activities in high dust areas will expose them to elevated levels of both inhaled and ingested manganese, and Dorman et al (2000) have recently shown that neonatal rats administered manganese orally may be at greater risk for Mn-induced neurotoxicity than adult rats.

Most of the data pertaining directly to the benefits issue come from occupational studies. Table 2 gives the details of some of the important studies that attempted to relate exposure to neurobehavioral endpoints. The mean blood concentrations of exposed workers, except for Chia et al (1993), hover near 10 : g/L, with their controls at one-half to two-thirds that value. Chia et al, however, studied a population in Singapore whose dietary habits undoubtedly differed from those in the other studies. Table 3 compares the results of a number of studies based on neurobehavioral endpoints. What is most evident there is the apparent sensitivity of motor function tests to manganese exposure, a result consistent with the evidence showing the main sites of deposition to lie in the basal ganglia, particularly the globus pallidus. Table 4 (Lucchini et al, 1999) offers more recent data from the population studied by Lucchini et al (1995). It too shows that mean control blood values are two-thirds of exposed values, meaning that an elevation

of one-third above baseline accounts for the performance differences between the two populations of workers. Also, note the closely overlapping ranges. Figure 3 plots the relationship in this population between air concentration and blood level in the work environment. Two features deserve comment. One is that even negligible air concentrations are associated with blood levels, as noted above, not overwhelmingly different from much higher concentrations. The second is that, at least in these workplaces, the distribution of exposure, as the authors note, is log-normal, with most workers clustered at the low end.

Worker populations present special problems for risk assessment. The healthy worker effect, a notorious confounder in epidemiological investigations, reduces the accuracy with which occupational data can be extrapolated to groups such as children, the elderly, or other especially susceptible populations. Moreover, standards such Threshold Limit Values and Permissible Exposure Limits are based on 8-hour days and 40-hour weeks rather than continuous environmental exposure. To more directly determine potential manganese toxicity in the general population, Mergler et al (1999) undertook a community study in southwest Quebec. The subjects ranged from 20 to 69 years of age and had not experienced any workplace exposures. The entire study sample of 297 subjects was about equally divided between men and women.

Table 5 presents the blood values. They show slightly higher levels in the women than in the men, but totally overlapping ranges. The investigators administered the most extensive series of neurobehavioral tests ever used to study manganese, and based most of their analyses on a separation of subjects based on blood levels. A value of 7.5 ：g/L served as the dividing concentration. Age was chosen as a second dichotomous variable separating subjects below and above 50 years of age.

The neuropsychological measures adopted by Mergler et al (1999) and that documented evidence of adverse effects are listed in Table 6. The first four are indices of motor function and the first three are described at length by Beuter et al (1999). The motor function measures yielded convincing relationships, but their most interesting features are their dependence on age. Figure 4 displays the interaction between manganese blood level (above or below 7.5 ：g/L) and age (above or below 50 years) for the index used to describe performance on a task requiring the subject to alternate strikes with a stylus at two spatially separated targets. This pattern, showing a persuasive influence of age, is consistent with most of the data from this study.

Neurodegenerative diseases, like most other degenerative diseases, are typically diseases of aging, with both incidence and prevalence rising with advancing age. One useful way to contemplate the potential impact of neurotoxic chemicals is to evaluate how they might shift the relationship between prevalence and age. A model of how even small shifts in a population distribution

can incur large public health costs is seen in Figure 6. It depicts the consequences of a 3-point or 3% shift in mean IQ score, the kind of shift produced by small elevations in lead exposure. It shows that even that small a shift produces a significant increase in the number of individuals classified as mentally retarded. It incurs massive expenses in remedial care and education, but also produces a significant decrease in the number of individuals in the superior range (e.g., IQ>130). Figure 7 shows that even a 1% leftward shift, or one IQ point, is a significant societal burden. In its evaluation of the benefits stemming from the removal of lead from gasoline, EPA, basing its calculations on the relationship between IQ score and lifetime earnings, estimated benefits approximating one trillion dollars.

A variation of this logic can be applied to manganese given the assumption that it can contribute to neurodegenerative disease. First, consider Figure 8, which depicts the reduction in nerve cell density with age that occur in certain brain structures. McGeer et al (1988) plotted the relationship between age and nerve cell number in the substantia nigra (SN). A key pathological marker of PD is loss of pigmented neurons in one part of SN. Figure 8 demonstrates that an acceleration of this natural loss by 0.1% annually will, over several decades, produce what might be termed premature aging of this structure. If the natural course of aging produces a loss of 40% by age 73, say, an additional acceleration of 0.1% will incur such a loss about ten years earlier.

Assume exposure to an agent that produces such a superficially minor acceleration. Figure 9 shows the consequences for the prevalence of PD of accelerations of 5 and 10 years respectively. The consequences are hardly minor. Table 7 takes the prevalence figures on which Figure 9 is based, and, from the projected US age distribution (US Census) in 2005, shows the baseline rates of PD and their estimated medical costs, and compares them to what would be expected if the age distribution were to be shifted by five years. The differences are considerable, and would result from an acceleration of functional loss of less than 0.1% annually (see Figure 8). For the age group 60-64, the increment in annual costs is over 700 million dollars.

Would this be a reasonable model for manganese? Or, put another way, what evidence is there to support a contribution by manganese exposure to PD or other neurodegenerative diseases?

One source of evidence is manganese poisoning, which confirms that manganese is a powerful neurotoxicant, producing the kinds of clinical signs, largely irreversible, listed in Table 1. A second source of evidence comes from detailed studies both of communities and of workers indicating that exposed populations displaying no signs of clinical disease can nevertheless be shown to suffer from neuropsychological deficits detected by appropriate testing procedures. But this kind of evidence is not specific to PD.

What is specific to PD, however, is both research and experimental data implicating the central nervous system structures targeted by manganese in PD. To incorporate these results into a benefits analysis first requires some probing into the potential relationship between manganese and neurodegenerative disease. It will be especially illuminating to examine how it might relate to PD because it is a clear example of a relationship with age. As noted earlier, the globus pallidus, on the basis of both chemical analyses and MRI, appears to accumulate manganese in greater quantities than other basal ganglia structures and is the site of lesions produced by manganese in appropriate doses. Although neuropathology does not indicate manganese-induced damage to the structure directly implicated in PD, the pars compacta of the substantia nigra, a great deal of evidence links its function with the globus pallidus.

One measure of the critical role played by GP in PD is the burgeoning literature on attenuation of PD symptoms by pallidal surgery or stimulation. Electrical stimulation of the internal pallidum may reduce the fluctuations associated with medication such as L-dopa, and permit a reduction in dosage. Pallidal surgery is now an accepted method for bringing substantial relief to PD patients. In addition, electrophysiological studies indicate a role for the globus pallidus in the resting tremor displayed by PD patients. Figure 5 shows the linkages among various basal ganglia structures and emphasizes the lack of isolation among them.

One conclusion to be drawn from this information is that what are called extrapyramidal diseases possess commonalities arising from their intimate and extensive structural and chemical interconnections. Damage to one component of the basal ganglia almost surely is bound to exert influence on functions subserved by other structural components, as in the overlapping symptoms of PD and Alzheimer's disease. In addition, the disabling effects of pharmacological therapies for PD, such as the dyskinesias resulting from L-dopa, are improved by pallidal stimulation, another source of evidence for the intimate links between GP and SN. A neat piece of evidence come from an experiment with monkeys (Zhang et al, 1999) rendered hemi-parkinsonian by an injection into the right carotid artery of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), originally discovered as a contaminant in designer drugs that produced parkinsonian signs in drug addicts. Figure 10 shows that monkeys with pallidal damage resulting from MPTP were less responsive to the amelioration of PD signs than monkeys lacking evidence of damage.

Both community surveys (Mergler et al, 1999) and studies of worker populations (e.g., Apostoli et al, 2000) suggest that relatively small increments in manganese blood levels are associated with significant diminutions in neurobehavioral function. If these functional indices are assumed to reflect deficits in brain function, and if we pair these deficits with the recognized declines in brain compensatory capacity associated with aging, slight elevations in

airborne manganese might produce a small, but medically and economically significant shift to an earlier onset of neurodegenerative diseases such as Parkinson's disease.

" Small" and "significant" need to be seen in context. An aging population is beginning to confront us with difficult medical and economic choices, and the most overwhelming problem is certain to be neurodegenerative diseases. In evaluating the potential contributions of environmental neurotoxicants to this problem, a simple calculation will prove illuminating. If the entrance of 30 patients into institutional care is delayed by one year, the savings amount to over one million dollars.

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